Supplementary webappendix

METHODS

Modified RECIST Criteria

RECIST 1·0 modifications

In addition to the RECIST 1·0 guidelines,[1] the following criteria were applied when determining tumours status:

- New lesions were required to have a minimum size of 10 mm in the longest diameter.[2] The finding of a new lesion was to be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumours. If a new lesion was equivocal, therapy was to be continued and follow-up evaluation was to be performed to clarify if it truly represented a new disease. Progression was declared once the lesion size became ≥10 mm.[3]
- If multiple new equivocal lesions (ie, more than one lesion) were found at any particular timepoint, the minimum size of 10 mm in the longest diameter was not required to determine progressive disease.
- If the new disease could not be measured, it must have had been unequivocal for progressive disease to be declared (eg, new skeletal lesions). New fluid collections required cytological confirmation of malignancy in order for progressive disease to be declared.
- For nontarget lesions, the following criterion was to be applied to determine "unequivocal progression": there must have had been an overall level of substantial worsening in nontarget disease, which was of a magnitude that even in the presence of stable disease (SD) or partial response (PR) in target disease, the treating physician would felt it important to discontinue study drug.[3]

Rationale for RECIST 1·0 modifications

Requirement of 10 mm minimum for longest diameter to be "new lesions": The appearance of a new lesion results in progressive disease (PD) per RECIST criteria.[1] In some instances (eg, liver), additional guidance regarding the detection of new "unequivocal" lesions is important.

The characterization of new liver lesions in NET is technically challenging, due to poor visualization of the lesions based on the enhancement patterns with contrast, prior embolization/local treatment of lesions and in some cases, liver steatosis. Requiring a minimum longest diameter of 10 mm will ensure the lesion is unequivocal (of note, similar criterion has been adopted in hepatocellular carcinoma [HCC], due to the complexity in the computed tomography (CT) or magnetic resonance imaging assessment (MRI) of the liver in

the context of hypervascular tumours, prior local therapies and/or underlying liver disease). If the lesion is equivocal due to its small size (ie, <10 mm in longest diameter), therapy should be continued and additional follow-up evaluations will clarify if it truly represents a new lesion.[2] If follow-up scans confirm that there is definitely a new lesion (eg, there is an increase in size), then progression should be declared once the lesion becomes unequivocal (ie, once the size reaches ≥ 10 mm).

Multiple lesion criteria: If multiple (more than one) new lesions appear at a given assessment, the finding is very unlikely to represent something other than tumours progression; therefore, it is considered unequivocal. In this scenario, minimum size criterion does not apply.

Expedited Central Review Process

All patients who have had disease progression determined by the local investigator required an expedited tumour response review by the central radiologist. The investigator seeking an expedited review had to indicate this request on the radiology referral form sent to the imaging contract research organization. The imaging contract research organization ensured that the central radiologists involved were also blinded to the expedited status of the reading. Rapid image transmission to the central radiologist was accomplished by uploading all digital images acquired by the investigator in a secured website. The central radiologist performed an expedited review of radiological images within 5 business days from the time of receipt of images by the imaging contract research organization. While the investigator was waiting for the results of the central review, it was preferable that the patient was continued on the study treatment. During this time, the investigator was responsible to do whatever is medically necessary for the patient. If after the central radiological review, there was an agreement in the assessment of disease progression between local and central radiology reviews, then the patient was discontinued from the study treatment and subsequent follow-up tumour assessments after discontinuation of study treatment were no longer required. If after the central radiologist review, there was discordance between local and central radiology determination of disease progression, the patient was to be continued to receive the study treatment unless there was a medical need (ie, rapid progression or clinical deterioration) for an immediate change in therapy. Patients continued to have scans performed as per protocol until the central radiologist's confirmation of disease progression or until initiation of further antineoplastic therapy.

Objective Response Rate and Disease Control Rate

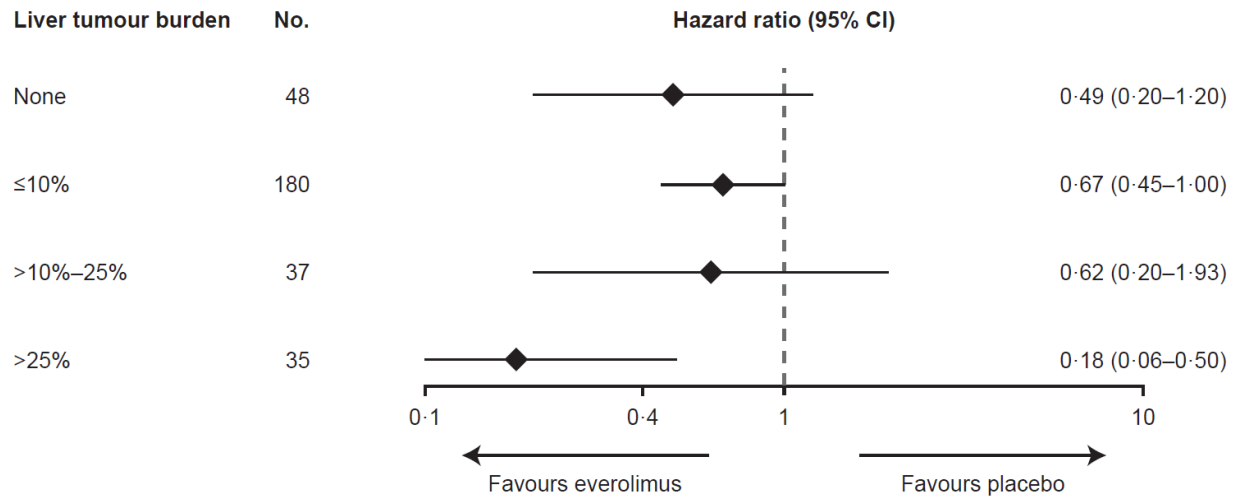
Objective response rate (ORR) was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR). ORR was calculated based on the full analysis set (ie, all patients who underwent randomization) using central radiological tumour assessment. Proportions of patients with ORR were presented by treatment group along with exact 95% confidence intervals.[1] The Cochran-Mantel Haenszel chi-square test (stratified by the three stratification factors considered for randomization) was used to compare the two treatment groups with respect to the ORR at one-sided 2·5% level of significance. The same analysis was performed for disease control rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD.

Overall Survival Analysis

The analysis of OS was to be performed if the primary endpoint PFS was statistically significant using a group sequential design with a log-rank test and three looks (Lan-DeMets group sequential design with O'Brien-Fleming type boundary at one-sided 2·5% level of significance). The first interim analysis was planned at the time of PFS primary analysis, followed by a second interim analysis when 50% information fraction was achieved. A total of 191 deaths were required to be observed in order to detect a HR of 0·65 with an 80% cumulative power, which correspond to an improvement from 30 to 46·2 months of the median OS.

RESULTS

Figure S1. Progression-free survival by liver tumour burden, central review (full analysis set).



Forest plot shows the effect of study treatment in subgroups defined according to liver tumour burden. Hazard ratio is obtained from unstratified Cox model.
CI=confidence interval.

Table S1. Best overall response assessed by central radiology review (full analysis set)

	Everolimus (N=205)	Placebo (N=97)
Best overall response		
Complete response	0	0
Partial response	4 (2·0)	1 (1·0)
Stable disease	165 (80·5)	62 (63·9)
Progressive disease	19 (9·3)	26 (26·8)
Unknown	17 (8·3)	8 (8·2)
Objective response rate, 95% CI	4 (2·0) [0·5–4·9]	1 (1·0) [0·0–5·6]
Disease control rate, 95% CI	169 (82·4) [76·5–87·4]	63 (64·9) [54·6–74·4]

Data are n (%) unless otherwise stated.

REFERENCES

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92**: 205–16.
2. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52–60.
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
4. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; **26**: 404–13.